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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,631	04/11/2005	Seiichi Araki	T0509.70011US00	5167

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WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
GRAFFEO, MICHEL	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/506,631	ARAKI ET AL.	
	Examiner	Art Unit	
	Michel Graffeo	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12 Nov 04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 1-12 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 17 January 2006.

Applicant's election with traverse of Group III in the reply filed on 17 January 2006 is acknowledged. The traversal is on the ground(s) that the Hird reference does not teach the use of riboflavin for the suppression of cytokines. This is not found persuasive because Hird teaches in paragraph 5 that riboflavin is an immunopotentiating compound and does indicate riboflavin as a medicament and therefore also demonstrates Group I lacks unity of invention since the composition is known in the art.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 13 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The phrases "Use of" and "The use of" constitute non-statutory claim language. In other words, the claimed recitation of a use,

without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). However, in order to advance prosecution these claims will be examined as method of use claims.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hypercytokinemia to the extent that there is shown an increased survival rate for an in vivo model treated with riboflavin as compared to the in vivo model not treated, does not reasonably provide enablement for the prevention of general hypercytokinemia nor for treatment without a specified endpoint. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation.

The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and ,
8) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1) the nature of the invention; the invention is directed to a method of treating and preventing hypercytokinemia but has not recited step(s) that (a) result in preventing nor (b) have a specified end result of the treatment.

2) the breadth of the claims; the scope of the method claims includes the prevention of hypercytokinemia in general with riboflavin, a derivative or salt thereof.

3) the predictability or unpredictability of the art; the ability of preventing all hypercytokinemia is not yet known in the art. The burden of enabling one skilled in the art to prevent hypercytokinemia would be much greater than that of enabling the treatment of such diseases. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the

objective of preventing hypercytokinemia. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for preventing hypercytokinemia.

No experimental evidence supporting the contention that the claim specified actives would actually prevent these diseases by simply administering the claim specified active agents has been demonstrated nor practice the invention without an envisaged endpoint or result of the treatment (not the absence of such recitation in the claim(s)). The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for preventing and for practicing same without a specific endpoint for the treatment of the claimed diseases.

The term "prevention" or "preventing" is synonymous with the term "curing" and both circumscribe methods of treatment having absolute success. Since absolute success is not as of yet reasonably possible with most diseases/disorders, especially those having etiologies and pathophysiological manifestations which are as complex/poorly understood as hypercytokinemia as recited in claims 13 and 15.

See for example, Tsuchida et al. Direct hemoperfusion by using Lixelle® column for the treatment of systemic inflammatory response syndrome. International Journal of Molecular Medicine. 10:485-488; 2002 which teaches an alternate method for removing cytokines from the blood suggesting that at the

time the application was filed there was no silver bullet for treating or preventing hypercytokinemia.

4) the amount of direction or guidance presented; the specification does not provide any guidance in terms of preventing hypercytokinemia. In particular, the Specification discloses a 7 out of 10 survival rate in Table 1, and a 6 out of 10 survival rate in Tables 2-3; however these are survival rates. Survival rates do not pre se demonstrate prevention along the line of not having occurred the first time.

5) the presence or absence of working examples; no working examples are provided for preventing hypercytokinemia, for example in a patient, in the specification. The applicant has not provided any competent evidence or disclosed any tests that are highly predictive for the preventative effects of the instant composition. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

6) the quantity of experimentation necessary; the quantity of experimentation would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. To support a claim to prevention or the like, Applicant

would need to provide confirmative in vivo data supporting the prevention of the disease as well as a method and dosage regime resulting in the prevention of same.

In view of the breadth of the claims, the chemical nature of the invention and unpredictability of preventing hypercytokinemia, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

In consideration of each of factors 1-6, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 provides for the use of at least one riboflavin, but, since the claim does not set forth any steps involved in the method/process, it is unclear what

method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 15 fails to recite a specified end point for the treatment and it is not apparent from the claim step(s) whch one set of steps would have resulted in "preventing" the disease state.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,814,632 to Araki et al. in view of Blomberg et al. Post-transplant cytokine monitoring. ASHI Quaterly; First Quarter (2001) (cited to show state of the art).

Araki et al. teach an immunopotentiating compound comprising riboflavin and derivatives thereof to treat infection (in current claims 13 and 15; see Abstract). The reference defines immunopotentiating as enhancing immune function for example as applied to organ transplants. Blomberg et al. teach that an increase in cytokines (a.k.a. hypercytokinemia) is associated with organ transplants and monitoring of same is important for proper adjustments to immunosuppression following grafts and for graft acceptance (see col 2 first paragraph and col 3 last paragraph). One of ordinary skill in the art would have found it obvious that riboflavin is useful in organ transplants because it reduces the amount of cytokines released by the host; a necessary function of allograft acceptance as discussed in Blomberg et al. Thus, reference teaches and makes prima facie obvious how to use the claimed invention at the time that it was made.

Claims 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grimble RF. Effect of antioxidative vitamins on immune function with clinical applications. Int J Vitam Nutr Res. (1997); 67(5):312-20.

Grimble teaches that antioxidative vitamins such as riboflavin prevent increased cytokine production via the glutathione production pathway (in current claims 13 and 15; see Abstract). One of ordinary skill in the art would have found it obvious that a

reduction in cytokines would be efficacious in the treatment of hypercytokinemia. Thus, reference teaches and makes prima facie obvious how to use the claimed invention at the time that it was made.

Claims 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grimble RF. Effect of antioxidative vitamins on immune function with clinical applications. Int J Vitam Nutr Res. (1997); 67(5):312-20 as applied to claims 13 and 15 above and further in view of Sammon. Dietary linoleic acid, immune inhibition and diseases. Postgrad Med J 1999; 75:129-132.

Grimble teaches that antioxidative vitamins such as riboflavin prevent increased cytokine production via the glutathione production pathway (in current claims 13 and 15; see Abstract). One of ordinary skill in the art would have found it obvious that a reduction in cytokines would be efficacious in the treatment of hypercytokinemia. Thus, reference teaches and makes prima facie obvious how to use the claimed invention at the time that it was made.

Sammon teaches that a lack of riboflavin causes an increase in cytokine production by modulating the glutathione production pathway which in turn causes an increase in PGE2 and cytokine production (in current claims 13 and 15; see Abstract and page 130).

One of ordinary skill in the art would have been motivated to combine the above references and as combined teach the claimed invention as claimed. One of ordinary skill in the art would have been motivated to combine Grimble and Sammon because

both are directed to riboflavin's effect on the glutathione production pathway and cytokine production. Sammon and Grimble compliment each other in that Grimble teaches the effects of riboflavin and Sammon supports Grimble by discussion the effects when there is a lack of riboflavin. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 13 and 15 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-20 of copending Application No. 10/472621. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully claimed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method of treating hypercytokinemia comprising riboflavin wherein the '621 application claims a method for immunostimulation which when read in light of the diseases treated i.e. sepsis covers a method of administering riboflavin wherein hypercytokinemia will necessarily be treated as well in light of Grimble which teaches that antioxidative vitamins such as riboflavin prevent increased cytokine production via the glutathione production pathway. One of ordinary skill in the art would have found it obvious that a reduction in cytokine would be efficacious in the treatment of hypercytokinemia and consequently sepsis. Thus, the combined references teach and make prima facie obvious how to use the claimed invention at the time that it was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

13 March 2006
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MG

Christopher S. F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600